Molecular Theory of Hydrophobic Effects: "She is too mean to have her name repeated."*

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ABSTRACT: This paper reviews the molecular theory of hydrophobic effects relevant to biomolecular structure and assembly in aqueous solution. Recent progress has resulted in simple, validated molecular statistical thermodynamic theories and clarification of confusing theories of decades ago. Current work is resolving effects of wider variations of thermodynamic state, *e.g.* pressure denaturation of soluble proteins, and more exotic questions such as effects of surface chemistry in treating stability of macromolecular structures in aqueous solution

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INTRODUCTION

In the past several years there has been a breakthrough, associated with the efforts of a theoretical collaboration at Los Alamos(1–11) but with important antecedents(12–16), on the problem of the molecular theory of hydrophobic effects. That breakthrough is the justification for this review.

One unanticipated consequence of that work has been the clarification of the 'Pratt-Chandler theory'(17). Judged empirically, that theory was not less successful than is typical of molecular theories of liquids. But the supporting theoretical arguments had never been compelling and engendered significant confusion. That confusion was signaled already in 1979 by the view(18): "The reason for the success of their theory may well be profound, but could be accidental. We cannot be sure which." Today the correct answer is 'both,' though accidental first. In an amended form, it is a compelling theory. In reviewing these developments, a significant volume of intervening theoretical work must eventually be viewed again in this new light. In addition, the work that clarified the Pratt-Chandler theory suggested several improvements and extensions, and was deepened by the parallel development of the molecular quasi-chemical theory of solutions(11, 19–23). On this basis, I predict an extended period of consolidation of the theory of these systems and inclusion of more realistic, interesting, and exotic instances.

An attitude of this review is to respect a scholarly patience in addressing the

foundations without prejudging the speculations ellicited by the fascinating biophysical motivations. Thus, physical chemists working at strengthening those foundations are the audience for this review.

Nevertheless, clarity of the biophysical goals is important. Thus, an uncluttered expression of the motivation and the basic problem is essential. The molecular theory of hydrophobic effects is an unsolved facet of a molecular problem foundational to biophysics and biochemistry: the quantitative molecular scale understanding of the forces responsible for structure, stability, and function of biomolecules and biomolecular aggregates. I estimate that the term 'hydrophobic' appears in every biophysics and biochemistry textbook. An intuitive definition of hydrophobic effects is typically assumed at the outset. Hydrophobic effects are associated with demixing under standard conditions of oil-like materials from aqueous solutions. A more refined appreciation of hydrophobic effects acknowledges that they are a part of a subtle mixture of interactions that stabilize biomolecular structures in aqueous solution over a significant temperature range while permitting sufficient flexibility for the biological function of those structures.

Preeminent characteristics of these hydrophobic interactions are temperature dependences, and concurrent entropies, that can be exemplified by cold denaturation of soluble proteins(24). If hydrophobic effects stabilize folded protein structures, then folding upon *heating* suggests that hydrophobic interactions become *stronger* with increasing temperature through this low temperature regime. This is a counter-intuitive observation.

A primitive correct step in relieving this contrary intuition is the recognition that water molecules of the solution participate in this folding process(25). Specific participation by small numbers of water molecules is not unexpected but also isn't the mark of hydrophobic effects. For hydrophobic effects, on the contrary, a large collection of water molecules are involved nonspecifically. It is the statistics of the configurations of these water molecules at the specified temperature that lead to the fascinating entropy issues. Because of the significance of these entropies, hydrophobic effects are naturally a topic for molecular statistical thermodynamics.

Given the acknowledged significance of this topic, it is understandable that the literature that appeals to them is vast. Many researchers from a wide range of backgrounds and with a wide variety of goals have worked on these problems. Thus, the 'unsolved' assertion will challenge those researchers. But the 'unsolved' assertion also reflects a lack of integration of principles, tools, and results to form a generally accepted mechanism of hydrophobic effects. For example, it is widely, but not universally, agreed that the hydrogen bonding interactions between water molecules are a key to understanding hydrophobic effects. Conventional molecular simulation calculations with widely accepted molecular interaction models

for small hydrophobic species in water broadly agree with experimental results on such systems(26–134). In this sense, everything is known. Nevertheless, this complete knowledge hasn't achieved a consensus for a primitive mechanism of hydrophobic effects. By 'mechanism' we mean here a simpler, physical description that ties together otherwise disparate observations. Though this concept of mechanism is less than the complete knowledge of simulation calculations, it is not the extreme 'poetic "explanation"' famously noted by Stillinger(135). The elementary simplifications that lead to a mechanism must be more than rationalizations; they must be verifiable and consistent at a more basic level of theory, calculation, and observation.

The 'breakthrough' mentioned in the first paragraph is particularly exciting because it hints at such a mechanism for the most primitive hydrophobic effects. A great deal more reseach is called for, certainly. But discussion of that development is a principal feature of this review.

WHAT CHANGED

The breakthrough required a couple steps. The first step was the realization that feasible statistical investigations of spontaneous formation of atomic sized cavities in liquid solvents should shed light on operating theories of hydrophobic hydration(12–15,136). Those studies could be based upon the formal truth(3,10)

$$\Delta\mu_{\rm A} = -RT \ln p_0 \tag{1}$$

where $\Delta\mu_{\rm A}$ is the interaction contribution to the chemical potential of a hard core hydrophobic solute of type A, and p_0 the probability that an observation volume defined by the excluded volume interactions of A with water molecules would have zero (0) occupants. These cavity formation studies were not an attempt to calculate hydration free energies for realistic hydrophobic solutes. The goal was just to examine simple theories and to learn how different solvents might be distinguished on this basis.

The 'small size' hypothesis

There was also a significant physical idea alive at the time those studies were undertaken(12): "The low solubility of nonpolar solutes in water arises not from the fact that water molecules can form hydrogen bonds, but rather from the fact that they are small in size." As a simple clear hypothesis, this view contributed to the breakthrough although the hypothesis was eventually disputed(13,137).

Packing and molecular sizes are important concerns for liquids because they are dense. The idea was that since water molecules are smaller than, say, CCl_4 molecules, the 'interstitial' spaces available in liquid water would be smaller than those in liquid CCl_4. The first disputed point was that this hypothesis was

suggested by the approximate scaled particle model(138, 139) and that model was known to have flaws(135, 140) as applied to hydrophobic hydration. The second disputed point was that treatment of the coexisting organic phase, liquid CCl_4 in this discussion, was less convincing than the treatment of liquid water: the modeling of a CCl_4 molecule as a simple ball is an oft-convenient canard but shouldn't be taken too literally. Another significant consideration is that liquid water is less dense on a packing fraction basis than most coexisting organic solvents.

Eventually(13–15, 136), the direct investigations at the low pressures of first interest indicated that the probable spontaneously occurring cavities might be smaller in typical organic solvents than in water, though the differences are small. What was decidedly different between water and organic solvents was the flexibility of the medium to open cavities larger than the most probable size. Water is *less* flexible in this regard, stiffer on a molecular scale, than typical organic liquids. Fig. 1 gives a macroscopic experimental perspective on this relative stiffness. Furthermore, the results for the organic phase were not at all similar to what scaled particle models suggested(14, 15). So as an explanation of the distinction between water and common organic solvents, the 'small size' mechanism must be discounted(91, 141–143). Nevertheless, we can anticipate subsequent discussion by noting that the equation of state of the solvent is important in establishing thermodynamic signatures of hydrophobic hydration.

Transient cavities probing packing and fluctuations

As an analysis tool for assessment of packing in disordered phases, studies of cavity statistics should be more widely helpful(23, 39, 46, 78, 86, 88, 99, 105, 112, 133, 145–155). The interesting work of Kocher, *et al.*, (148) is notable. Those calculations studied the cavity formation work in protein interiors and that cavity formation work was seen to be larger than for comparable organic solvents. In that respect, the packing of those protein interiors was tighter, less flexible, than a simple oil droplet. This conclusion seems significant for our pictures of protein structures and deserves further investigation. Structural and compositional heterogeneity are undoubtedly also important features of the cores of globular proteins. These observations should be helpful in distinguishing the interiors of micelles from the cores of folded globular proteins(156).

Modeling occupancy probabilities

The decisive second step in achieving the present breakthrough was the modeling of the distribution p_n of which p_0 is the n=0 member(1). Several specific distributions p_n had been tried in analyzing the results of Pratt and Pohorille(14). But it was eventually recognized that a less specific approach, utilizing a maximum en-

tropy procedure to incorporate successively more empirical moment information, was prudent and effective. Surprisingly, direct determination of the distribution p_n showed that a two moment model

$$-\ln p_n \approx \zeta_0 + \zeta_1 n + \zeta_2 n^2 \tag{2}$$

was accurately born-out in circumstances of computer simulation of liquid water(1). The parameters ζ_j are evaluated by fitting of the predicted moments $\langle n^j \rangle$, j = 0, 1, ... to moment data. A practical virtue of this two moment model is that the required moment data can be obtained from long-available experimental results. A further surprise was that it had previously been shown, in different contexts and with additional assumptions(16, 157), that theories of a Percus-Yevick analog type had a structure derivable from a Gaussian or harmonic density field theory. The Pratt-Chandler theory was of this Percus-Yevick analog type. To the extent that the empirical observation Eq. 2 suggests a normal distribution, the Pratt-Chandler theory is given a better foundation than was available at its genesis(10).

Non-equivalence with Pratt-Chandler theory

In fact, the two moment model Eq. 2 is *not* precisely the same as the Pratt-Chandler theory. There are several related direct observations that can make that point clear. For example, the probability model Eq. 2 assigns probability weight only to non-negative integer occupancies. That is not the case for the harmonic density field theory. The restriction that such density field theories should not permit the negative occupancy of any subvolume is an obvious but interesting requirement. Additionally, the Percus-Yevick theory for hard sphere mixtures can predict *negative* probabilities(158). These are technical issues, however, and the performance of the two moment model Eq. 2 gives strong and unexpected support for the Pratt-Chandler theory.

There is a different respect in which the correspondence of the two moment model Eq. 2 with the Pratt-Chandler theory is imprecise. The kinship indicated above is based upon calculation of hydration free energies when the solvent can be idealized as a harmonic density field. That can be straightforwardly carried over to consideration of nonspherical solutes. For example, classic potentials of mean force might be addressed by consideration of a diatomic solute of varying bond length. The Pratt-Chandler theory does not do that directly but utilizes the structure of the Ornstein-Zernike equations together with yet another Percus-Yevick style closure approximation. Those distinctions have not yet been discussed fully.

'Good theories are either Gaussian or everything'

A curious feature of the $\ln p_n$ moment modeling is that convergence of predictions for $\Delta\mu_{\rm A} = -RT \ln p_0$ with increasing numbers of utilized moments is non-monotonic(6, 8, 10). The predicted thermodynamic results are surprisingly accurate when two moments are used but become worse with three moments before eventually returning to an accurate prediction with many more moments available. The two moment model, and also the Pratt-Chandler theory, is fortuitous in this sense. But this does conform to the adage that 'good theories are either Gaussian or everything.'

TECHNICAL OBSERVATIONS AND EXTENSIONS

The theory above has always been understood at a more basic level than the description above(10). The most important observation is that the Mayer-Montroll series(10, 159) can be made significantly constructive with the help of simulation data(10, 13, 136) and those approaches can be more physical than stock integral equation approximations. Simulation data can provide successive terms in a Mayer-Montroll series. In that case the binomial moments $\langle \binom{n}{j} \rangle_0$ are the stylistically preferred data(10). Then the maximum entropy modeling is a device for a resummation based upon a finite number of initial terms of that series(10). Several additional technical points are helpful at this level.

Default Models

The adage that 'good theories are either Gaussian or everything' is serious but doesn't address the physical reasons why these distributions are the way they are. In fact, painstaking addition of successive moments is not only painful but often unsatisfying. And the two moment model Eq. 2 has been less satisfactory for every additional case examined carefully beyond the initial one that was connected with this breakthrough(1); recent examples can be seen in Ref. (23, 133). It is better to consider simple physical models for the distribution p_n and approximations

$$-\ln\left[\frac{p_n}{\hat{p}_n}\right] \approx \zeta_0 + \zeta_1 n + \zeta_2 n^2 + \ldots \tag{3}$$

where $\hat{p}_n$ is a model distribution chosen on the basis of extraneous considerations. Since $p_n = \hat{p}_n$ in the absence of further information, $\hat{p}_n$ is called the default model. Utilization of a default model in this way compromises the goal of predicting the distribution and instead relies on the moments to adapt the default model to the conditions of interest. The default model of first interest(1) is $\hat{p}_n \propto 1/n!$ This default model produces the uncorrelated result (the Poisson distribution) when the only moment used is $\langle n \rangle$. Another way to identify default models is to use probabilities obtained for some other system having something in common with the aqueous solution of interest(8).

An important practical point is that this approach works better when the default model is not too specific(22). This can be understood as follows: The moment information used to adapt the default model to the case of interest is not particularly specific. If the default model makes specific errors, a limited amount of that nonspecific data will not correct those errors adequately. This argument gives a partial rationalization for the accurate performance of the flat default model that leads to Eq. 2.

In Eq. 2 $\zeta_0 = \Delta\mu_{\rm A}/RT$ but it is helpful to notice that this thermodynamic quantity can be alternatively expressed as(10)

$$\Delta\mu_{\rm A} = RT \ln \left\{ 1 + \sum_{n=1} \left(\frac{\hat{p}_n}{\hat{p}_0} \right) \exp \left[- \sum_{k=1}^{k_{max}} \zeta_k \binom{n}{k} \right] \right\} \tag{4}$$

where binomial moments through order k_{max} are assumed and the default model is included. ζ_0 does not appear on the right since that normalization factor is being expressed through the thermodynamic property. The point is that this is a conventional form of a partition function sum. The interactions are n-function interactions, in contrast to density or ρ-functional theories, but with strength parameters adjusted to conform to the data available. The fact that $\Delta\mu_{\rm A}$ is extracted from a fully considered probability distribution, and this consequent structure, is the substance behind our use of the adjective 'physical' for these theories. These theories are still approximate, of course, and they will not have the internal consistency of statistical mechanical theories obtained by exact analysis of a mechanical Hamiltonian system.

Quasi-chemical theory

The quasi-chemical theory(11,19) adapted to treat hard core solutes(23) gives an explicit structure for the $\Delta\mu_{\rm A}$ formula as in Eq. 4. That result can be regarded as a formal theorem

$$\Delta\mu_{\rm A} = RT \ln \left[1 + \sum_{m \geq 1} K_m {\rho_{\rm W}}^m \right] \ . \tag{5}$$

The K_m are equilibrium ratios

$$K_n = \frac{\rho_{\bar{\rm A}{\rm W}_{\rm n}}}{\rho_{\bar{\rm A}{\rm W}_{\rm n=0}} {\rho_{\rm W}}^n} \tag{6}$$

for binding of solvent molecules to a cavity stencil associated with the AW excluded volume, understood according to the chemical view

$$\bar{\rm A}{\rm W}_{\rm n=0} \ + \ {\rm nW} \rightleftharpoons \bar{\rm A}{\rm W}_{\rm n} \ . \tag{7}$$

$\bar{\rm A}$ is a precisely defined cavity species(23) corresponding to the AW excluded volume. Eq. 4 should be compared to Eq. 5; because of the structural similarity, it

is most appropriate to consider Eq. 4 as a quasi-chemical approximation. The K_m are well-defined theoretically(23) and observable from simulations. So again this approach can be significantly constructive when combined with simulations(11, 19, 20). But the first utility is that the low density limiting values of K_m, call them ${K_m}^{(0)}$, are computable few body quantities(23). The approximation

$$\Delta\mu_{\rm A} \approx RT \ln \left[1 + \sum_{m\geq 1} {K_m}^{(0)} {\rho_{\rm W}}^m e^{-m\zeta_1} \right] \tag{8}$$

is then a simple physical theory, the primitive quasi-chemical approximation(23). The Lagrange multiplier ζ_1 serves as a 'mean field' that adjusts the mean occupancy to the thermodynamic state of interest. For a hard sphere solute A in a hard sphere solvent, this theory produces sensible results though it does not achieve high accuracy in the dense fluid regime $\rho d^3 > 0.7$(23) where d is the diameter of the solvent hard spheres. [The foremost questions for aqueous solutions are at the lower boundary of this conventional demarcation of dense fluids.] When the accuracy of this theory for hard sphere systems degenerates, it is because the distribution

$$\hat{p}_n = \frac{{K_n}^{(0)} {\rho_{\rm W}}^n e^{-n\zeta_1}}{1 + \sum\limits_{m\geq 1} {K_m}^{(0)} {\rho_{\rm W}}^m e^{-m\zeta_1}} \tag{9}$$

is too broad in the low n extreme(23); see Fig. 2. Because this theory thus directly treats short range molecular structure but somewhat too broadly, it is a natural suggestion for generating default models. No direct experience along those lines is presently available.

The investigation of how such a simple theory breaks Eq. 9 down is a yet more interesting aspect of the development of the quasi-chemical theories for these problems(11,23). For the hard sphere fluid at higher densities the primitive quasi-chemical theory Eq. 9 remains a faithful descriptor of the n≥1 features of the distribution. But the actual p_0 (see Fig. 2) becomes depressed relative to the model; p_0 breaks away from the rest of the primitive quasi-chemical distribution. In fact, the suggested correlation correction can be effectively empiricised and provides an accurate description of these distributions for hard sphere fluids. These exotic complexities with p_0 are not reflected in Eq. 2. Tiny features like that were noticed, however, in the initial simulation studies of these probability models(1). Additionally, we anticipate discussion below by noting that proximity to a low pressure liquid-vapor transition point, associated with solvent-solvent attractive interactions and potential dewetting of hard surfaces, is expected to *increase* p_0(1, 11).

Importance sampling to correct occupancy probabilities

A more workman-like investigation of these theories can be based upon the potential distribution theorem(3, 23, 160)

$$e^{-\Delta\mu_A/RT} = \left\langle \left\langle e^{-\Delta U/RT} \right\rangle \right\rangle_0 \ . \tag{10}$$

The brackets $\langle\langle \ldots \rangle\rangle_0$ indicate the average of the thermal motion of a distinguished A solute and the solvent under the condition of no interactions between these subsystems; the latter restriction is conveyed by the subscript '0.' Distributions $\hat{p}_n$ should be helpful as importance functions. It would be natural to use this estimate to revise the calculation of all the probabilities p_n. But we have seen a case, Fig. 2, where the distinction between n=0 and n≥1 is most interesting. In addition, this quantity averaged here Eq. 10 takes the values zero (0) if n≥1 and one (1) for n=0. Thus we consider the importance function

$$W = \left\{ \begin{array}{c} \hat{p}_0, n = 0 \ , \\ 1 - \hat{p}_0, n > 0. \end{array} \right\} \tag{11}$$

The standard importance sampling ideas(161, 162) then produce

$$e^{-\Delta\mu_A/RT} = \frac{\left\langle \left\langle W \, e^{-\Delta U/RT} \right\rangle \right\rangle_{1/W}}{\langle\langle W \rangle\rangle_{1/W}} \ . \tag{12}$$

The sampling distribution is the Boltzmann weight in Eq. 10 multiplicatively augmented by the configurational function $1/W$ and corresponds to a finite probability step $\frac{p_0}{1-p_0}$ as the first solvent molecule enters the observation volume. Typically, this will lead to a diminished occupancy of the observation volume. After some rearrangement, Eq. 12 is

$$\frac{p_0 - \hat{p}_0}{\hat{p}_0} = \frac{(2\pi_0 - 1)}{1 - \pi_0 \left(\frac{1-2\hat{p}_0}{1-\hat{p}_0} \right)} \ . \tag{13}$$

Here π_0 is the probability of the observation volume being empty with the reweighted sampling

$$\pi_0 = \left\langle \left\langle e^{-\Delta U/RT} \right\rangle \right\rangle_{1/W} \ . \tag{14}$$

These formulae could be used directly with simulation calculations. The best available approximate p_0(135, 164) could be used as $\hat{p}_0$ in order to achieve higher accuracy; that would be interesting but not easy because achieving n≫ 0 → n=0 transitions requires rare collective processes. On the other hand, n=0→n≥1 transitions will have a low acceptance probability. But our argument here is directed toward understanding physical features left out of simple models such as the quasi-chemical model of Eq. 4. The choice here of W in Eq. 11 is transparently directed towards discussion of a 'two-state' picture of the hydration.

With that goal, the conceptual perspective is the more interesting one. This is a discrete example of a procedure common in density functional arguments. Local particle occupancies are altered by a reweighting. Just as with p_0, π_0 can be studied with a Mayer-Montroll series and moment modeling(10). The moments involved now would be obtained from study of the designed non-uniform system. The average on the right-side of Eq. 14 is a functional of the density induced by the reweighting.

For example, if the reweighting can serve to nucleate a bubble because of proximity of the thermodynamic state to a liquid-vapor transition, then, physically viewed, π_0 is expected to be composed of two important cases: (a) 'vapor' with a depletion region surrounding the observation volume; this gives contribution one (1) to π_0 for these cases and (b) 'liquid;' typically these cases will contribute zero (0) to π_0. But occasional configurations, roughly with frequency $\hat{p}_0$, will give $e^{-\Delta U/RT} = 1$. Thus as a rough estimate, we expect

$$\pi_0 \approx \frac{e^{-\Delta F/RT}(\frac{1-\hat{p}_0}{\hat{p}_0}) + \hat{p}_0}{e^{-\Delta F/RT}(\frac{1-\hat{p}_0}{\hat{p}_0}) + 1} \tag{15}$$

where ΔF is the free energy for formation of a bubble from the liquid corresponding to boundary conditions n=0 on the observation volume. That free energy might be approximated by a combination of van der Waals theories and molecular theories appropriate for the vapor phase(163). Let's consider a one phase, dense liquid thermodynamic state, not far from coexistance with a vapor phase so that $1 > e^{-\Delta F/RT} > \hat{p}_0$. With these estimates, Eqs. 13 and 15 evaluate to

$$p_0 \approx e^{-\Delta F/RT} > \hat{p}_0 \tag{16}$$

The insertion probability is the probability of bubble formation, surely the only simple guess, and this estimated change raises the value $\hat{p}_0$.

van der Waals picture

On the basis of the observations above, we can construct the following picture(23) by considering how these theories would work for an atomic size hard sphere solute in a simple van der Waals fluid system. Consider packing effects first, then subsequently the effects of attractive interactions. For dense liquid cases with full-blown packing difficulties, models such as Eq. 2 or 9 overestimate p_0 because those models aren't accurate for packing problems in the dense fluid regime. Next, consider attractive interactions and the possibility of dewetting. Those effects raise p_0. Models such as Eq. 2 do not reflect these phenomena. But these two errors can compensate, so Eq. 2 can be empirically accurate for atomic solutes despite the naivité. This is another rationalization of the astonishing, fortuitous accuracy of the two moment model and of the Pratt-Chandler theory.

While absorbing this argument, there are two additional points that may be noted. The first point is that in discussing errors in treating packing effects, we have been concerned about errors of the same type as those in the Percus-Yevick theory for the hard sphere fluid. But the Percus-Yevick theory of the hard sphere fluid might be considered *the* most successful theory of a liquid, "gloriously accurate, considering its simplicity"(166). So this discussion is bringing a high-sensitivity view to this problem. This is necessary because of the importance and high interest in these problems. The second point for note is that 'attractive interactions' in this argument involve solvent-solvent interactions, *not* solute-solvent attractive interactions. Part of the subtlety of these discussions is that the approach that offers models such as Eq. 2 is sufficiently empirical that a unique identification of the source of a particular inaccuracy is nontrivial.

HYDROPHOBIC HYDRATION AND TEMPERATURE DEPENDENCES

The most astonishing result of the new theory Eq. 2 is its explanation of the hydrophobic temperature dependence known as 'entropy convergence' (2, 9–11, 133) and those temperature dependences are discussed here.

Solubilities

The solubilities of simple gases in water have some interesting complexities(167). Many simple gases have a solubility minimum in water at moderate temperatures and pressures. Since the solubility is governed by $\Delta\mu_{\rm A}/RT$, the temperature variation of the solubility at a fixed pressure requests information on

$$\left(\frac{\partial \Delta\mu_{\rm A}/RT}{\partial T}\right)_p = -\frac{1}{T}\left(\frac{\Delta h_{\rm A}}{RT}\right) \tag{17}$$

with $\Delta h_{\rm A}$ the partial molar enthalpy change upon dissolution of species A and we considering the low concentration limit here. Thus, a solubility minimum leads us to anticipate a temperature of zero enthalpy change for the dissolution where $\Delta\mu_{\rm A}/RT$ plotted as a function of T has a maximum.

At a higher temperature the dissolution of many simple gases shows approximately zero partial molar entropy change:

$$\left(\frac{\partial \Delta\mu_{\rm A}}{\partial T}\right)_p = -\Delta s_{\rm A} \ . \tag{18}$$

$\Delta\mu_{\rm A}$ plotted as a function of T has a maximum. More puzzling is the fact that this temperature of zero entropy change is common to a number of different gases. This phenomenon is referred to as 'entropy convergence' because the entropies of hydration of different solutes converge to approximately zero at a common temperature(168, 169).

Model explanation

The puzzle "why?" was first answered on a molecular level in Ref. (2) on the basis of the model Eq 2; see also(9–11, 133). Establishing these two temperature behaviors should go a long way toward establishing the temperature variations of hydrophobic effects throughout an extended range relevant to biomolecular structure.

If we agree to be guided by an estimate of p_n based upon a continuous normal distribution(2, 9–11) then evaluation of the Lagrange multipliers of Eq. 2 is not a problem and

$$\Delta\mu_{\rm A}/RT \approx \frac{1}{2}\left\{\frac{\langle n\rangle_0{}^2}{\langle\delta n^2\rangle_0} + \ln[2\pi\langle\delta n^2\rangle_0]\right\} \tag{19}$$

$$= \frac{1}{2}\left\{\frac{(\rho v)^2}{\langle\delta n^2\rangle_0} + \ln[2\pi\langle\delta n^2\rangle_0]\right\} \tag{20}$$

with v the volume of the AW excluded volume, expected to be weakly temperature dependent. The surprise is that $\langle\delta n^2\rangle_0$ varies only slightly with temperature over the interesting temperature range. This is suggestive of the data shown in Fig. 1. Furthermore the second term of Eq. 20 is smaller than the first. Therefore the plot of $\Delta\mu_{\rm A}$ as a function of T experiences a maximum because the combination $T\rho^2$ has a maximum as $\rho = \rho_{sat}(T)$ decreases with increasing temperature along the coexistence curve. To the extent that the rightmost term of Eq. 20 can be neglected and $v^2/\langle\delta n^2\rangle_0$ is independent of temperature, then entropy convergence will occur and the temperature at entropy convergence will be the same for all hydrophobic solutes.

This development applies to model hard core solutes and the convergence temperature does appear to shift slowly but systematically to lower temperatures as the volume of the solute increases. But it was disturbingly noted nearly forty years ago that the success of the scaled particle model in evaluating hydration entropies "... suggests an almost thermodynamic independence of molecular structure"(140). In the entropy convergence phenomena, we see that this almost thermodynamic independence of molecular structure is a feature of the data(169) and that the current theory gives a simple molecular explanation that resolves that puzzle.

The lower temperature iso-enthalpy solubility minimum is expected to be tied to a different aspect of the solution-water interactions, the van der Waals attractive interactions. Following a WCA view, these effects should be reasonably described by first order perturbation theory so as a qualitative model we have(9,11)

$$\Delta\mu_{\rm A} \approx -A\rho + BT\rho^2 + CT \tag{21}$$

with fitting parameters A, B, and C. This equation does indeed have the correct qualitative behaviors(9, 11). If this Eq. 21 is used as a fitting model and

the parameters are unrestricted, it is essentially perfect. If the parameters are constrained by physical expectations for the temperature independent fitted parameters are v, $\langle \delta n^2 \rangle_0$, and A, then this model is only qualitatively and crudely successful in describing experimental solubilities.

Several of these considerations have been reexamined recently with results consistent with this picture(170, 171). Although these temperature behaviors were not always so clearly recognized as this, there remains specific solubility issues that aren't resolved including at the simulation level. An interesting case was provided by the important simulation calculations of Swope and Andersen(38) on solubility of inert gas atoms in water. With regard to the Lennard-Jones solute water (oxygen) interaction models, they concluded: "For the potentials used in the present simulations, it is not possible to fit the value, slope, and curvature for helium and neon without choosing what we believe to be unreasonably large values of σ. We can, however, obtain fits to the data for argon and krypton with reasonable values of the diameters." Simulation calculations for such cases have been pursued several times since then; those activities up to 1998 are summarized by Arthur and Haymet(106) and the latter effort also concludes with some ambiguity about the case of the He solute.

It is also important to emphasize that this model is used here only over a limited temperature range and at low pressure. Lin and Wood(95) used molecular dynamics to model the thermodynamic properties of small hydrocarbons in water over a wide range of temperature and pressure and Errington, *et al.*(109) studied the phase equilibria of water-methane and water-ethane systems of over wide ranges of temperature and pressure using Monte Carlo techniques.

RECENT EXPERIMENTAL STUDIES OF HYDRATION STRUCTURE

In recent years, efforts to measure directly the structure of water surrounding simple hydrophobic solutes have produced results that should be of quantitative relevance to the theories discussed here(100, 172–176). A more quantitative consideration is warranted but the initial impression is that these results are in good agreement with the calculations that have been done. These data give the weight of evidence to important basic conclusions also.

Pressure Dependence of Hydrophobic Hydration

One such conclusion is that this structuring of water appears to be independent of variations of the pressure to 700 bar (70 MPa)(175). This may be important to the current issue of pressure denaturation of soluble proteins as is discussed below. But investigation in a higher pressure range would be necessary for that purpose(119, 177).

'Clathrate' is in the eye of the beholder

Another important conclusion follows from the direct comparison of the radial distribution of oxygen atoms surrounding Kr in liquid aqueous solution and in a solid clathrate phase. Those radial distributions are qualitatively different in the two different phases. This is important because a 'clathrate' picture of hydration structure of nonpolar solutes in liquid water is a common view of hydrophobic hydration that has not been of quantitative relevance; it has been a 'pictorial theory'(178). In contrast, several theoretical calculations that have had quantitative value assume roughly the antithesis of 'clathrate,' that the conditional density of water surrounding of a non-spherical nonpolar solute can be built-up by superposition of proximal radial information(84, 85, 94, 179–181). The 'clathrate' language is widely used, hardly explicitly justified, and leads to misunderstandings. A number of studies have explicitly considered the issue of how valid is the 'clathrate' description(53, 55, 82, 108, 116, 182, 183). The conclusion seems to be that if you look for clathrate-style hydration structures you probably see them but if you ask whether they are necessary for a correct quantitative understanding, the answer is 'no.' 'Clathrate' is in the eye of the beholde. A reasonable recommendation is that when 'clathrate' is used as a descriptor in these liquid solutions, it should be explicitly defined and justified. Attempts to formulate quantitative theories on the basis of chemical models of these hydration shells are known but ill-developed(11).

POTENTIALS OF THE MEAN FORCES AMONG PRIMITIVE HYDROPHOBIC SPECIES IN WATER

The theories discussed above are straight-forwardly applicable to non-spherical solutes. For a solute composed of two atoms with varying interatomic separation, the comparison

$$\Delta\mu_{AA'}(r) - \Delta\mu_A - \Delta\mu_{A'} \equiv w_{AA'}(r) \tag{22}$$

leads to the classic issue of the 'potential of mean force' (pmf), an issue of long-standing interest(26, 51, 65, 68, 177, 184–196, 198–210, 212–216). The model Eq. 2 for a simple case was tested against simulation results(1) and the comparison was close. That theory, including Eq. 20, sheds new light on these properties.

Contact Hydrophobic Interactions

Consider $w_{AA}(r)$ for atomic solutes in contact. When the solute atoms are in van der Waals contact, we still anticipate that $\langle\delta n^2\rangle_0$ will be only weakly temperature dependent. Further, the volume excluded to the solvent by the pair is less than twice the volume of an atom alone because of the overlap of their

excluded regions. Thus the dominant contribution to Eq. 22 is negative, stabilizing the contact pair, and that stabilization increases with temperature below the entropy convergence temperature.

[Note that the subtraction Eq. 22 requires some additional thought when the logarithmic term of Eq. 20 is addressed(6). If the subtraction were naively carried-out, that r-independent nonzero difference might imply pathologically long-ranged interactions. A more careful consideration of the statistical approaches satisfactorily resolves that pathology(6). This detail shows again that these theories are not naively equivalent to the Pratt-Chandler theory.]

Non-contact Hydrophobic Interactions

On the other hand, when the atomic solutes are separated enough that a water molecule may fit between them, the volume excluded to the solvent by the pair is more nearly twice the excluded volume of the separated atoms. The theories following Eq. 2 then are more sensitive to water molecule correlations of longer range because the information $\langle \delta n^2 \rangle_0$ depends on those correlations. These theories then produce more subtle effects. Non-contact hydrophobic interactions may be, nevertheless, significant because of the larger configurational volume corresponding to those solvent-separated configurations. In addition, as discussed by Pratt and Chandler(217, 218), free energies of these solvent-separated configurations may be more sensitive to details of van der Waals attractive interactions than are contact configurations.

Simulation results

These views seem to be born out by the available simulation results, although(205) "the conclusions drawn from previous simulation calculations have been very contradictory." Substantial stability for contact hydrophobic pairs is probably the least contradictory of the possible conclusions. The recent preponderance of simulation results indicate that these contact pairs are stabilized by favorable hydration entropies(68, 201–203, 205, 206, 209, 216, 219). This would agree with the view established from the simple model Eq. 20 but those model temperature variations have been checked mostly along the liquid-vapor coexistence curve. The interesting results of Ref. (205,206) find substantial temperature variations at fixed water density. It was noted(203) that the conditions of temperature increase at fixed density strengthen the apparent entropic stabilization of the contact pair. That is also how Eq. 20 works; the density decrease serves to moderate the temperature increase and eventually, at the entropy convergence temperature, to dominate it. But the large effects seen by the Vienna group(205, 206) make it unclear that the simple model Eq. 20 will be accurate for those phenomena.

Simulation results for the solvent-separated configurations are less clear also.

There are entropic and enthalpic temperature effects in opposite directions with small net results(202, 206, 209). Because of the larger configurational volume for the solute pair in this configuration, these smaller hydration free energies are not negligible and(206) "the puzzling finding that the marked hydrophobic behavior of methane-like solutes concluded from the free energy data is not reflected in a similarly clear manner by the second osmotic virial coefficients requires a closer inspection of the underlying phenomena." See also (197). There is precedent, depending on a variety of additional details, for simulation results to exhibit either hydrophobic clustering or not, *i.e.*, "hydrophobic repulsion."(193).

Polarizability?

The complications suggested for these solvent-separated configurations seem to have lead to other contradictory results. It was suggested long ago(190) that solute polarizability might change the character of hydrophobic interactions predicted by simple theories. A later simulation calculation that included explicit polarizability(65) in the water-water interactions also suggested that these more complicated descriptions might qualitatively change the hydration of non-contact atom pairs. Further calculations again suggested that polarizability could lead to substantial changes but in a different direction from those seen earlier(204); treatment of long-ranged interactions was noted as a significant issue in these calculations. More recent studies of interaction models that include polarizability, however, have restored an original 'small change' view for the moment(209).

Alkane conformational equilibrium in water

The potentials of mean force just discussed are relevant to consideration of the conformational equilibrium of small flexible hydrophobic molecules in water. The first test case for theories has always been the *trans-gauche* isomerization of n-butane(84, 91, 179, 181, 220–226). For the case of n-butane, solvent separated possibilities are not available, so the contact hydrophobic interactions are relevant. The population of the more compact *gauche* configuration is enhanced by an entropic hydration effect. Hummer, *et al.,*(1) applied to the model of Eq. 2 to the case of conformational equilibrium of n-butane in water and found close agreement with the latest simulation results. Hummer has effectively adapted the model of Eq. 2 so that it can be simply applied to other alkanes(227). Much longer chain molecules that are strictly hydrophobic as less well studied primarily because they would be so unusual as isolated components of aqueous solutions. Hydrophilic groups are necessary to solubilize large molecules. Perhaps the simplest such soluble molecules would be polyethylene oxide chains which are a specific interest(228). But Gallicchio, *et al.,* (129) has recently studied the hydration of slightly larger alkanes in additional detail.

PRESSURE DEPENDENCE OF HYDROPHOBIC INTERACTIONS

The intense current interest in pressure studies of protein structure is due to the alternative light that this research can shed on protein conformational dynamics. A recent example can be found in (229) but we are unable to review adequately that body of interesting work here.

The complications of the non-contact hydrophobic interactions mentioned above appear to be involved in understanding pressure denaturation of proteins, however. We identify some of that work because views of hydrophobic effects had been paradoxical for these issues(230) and because it gives additional perspective into the theories discussed here. Wallqvist reported initial studies of pressure dependence of hydrophobic interactions(182,231). Remarkably, atomic hydrophobic solutes in water clustered at low pressure but dispersed at a substantially higher pressure that wasn't further quantified in that study. Later the Rutgers group took an important step(207) in Monte Carlo calculations of the effects of pressure on the pmf between Lennard-Jones model hydrophobic atomic solutes in water. Hummer, *et al.*(4) then developed the theory Eq. 2 for these pmfs as a function of pressure. That theory suggested that non-contact configurations of hydrophobic pairs become progressively more stable relative to contact pairs and that this might be a feature of pressure denaturation that was known to produce less disrupted structures than does heat denaturation. Subsequent molecular dynamics calculations(177) confirmed this picture of dispersal at higher pressures and the pressure variations of the pmfs: as pressure is increased, these pmfs become more structured, the contact minimum deepens, the desolvation barrier becomes higher, the solvent-separated well becomes better defined, deeper, and it appears to deepen faster than the contact well. This work also observed clustering of hydrophobic atomic solutes at low pressure (1 atm) but dispersal at high pressure (8000 atm, 810.6 MPa). This work also saw changes in the solute-water(oxygen) radial distribution that should be observable in experimental studies such as those of Ref. (175). But the simulation results are for considerably higher pressures than the experimental work reported. These calculations also considered spherical hydrophobic solutes of a larger size, more comparable with valine, leucine, or iso-leucine side chains. The responses to substantial pressure increases were similar but perhaps slightly more pronounced. A physical view is that as the pressure is increased, water molecules can be jammed between contact hydrophobic pairs; this evidently results in a more efficient, lower-volume packing, and consequently a negative hydration free energy change with increasing pressure for non-contact configurations.

SIZE DEPENDENCE OF HYDROPHOBIC HYDRATION FOR HARD SPHERE SOLUTES

For a hard sphere solute, the rate of increase of the hydration free energy Eq 1 with the distance of closest AO approach, denoted by λ, produces a particularly interesting quantity

$$\rho_W G(\lambda) = \frac{1}{4\pi\lambda^2}\left(\frac{\partial\Delta\mu_A/RT}{\partial\lambda}\right) \ . \tag{23}$$

This $\rho_W G(\lambda)$ is the conditional density of the solvent water (oxygen) at contact with the spherical solute. Because of the involvement of $\partial\Delta\mu_A/\partial\lambda$ this relation describes the compressive force exerted by the solvent on the solute.

Contact densities

Direct studies of these quantities have shown(14, 15) that in the range 2.0 Å< λ <3.0 Å $G(\lambda)$ for liquid water is approximately two-times larger than for n-hexane. Water exerts a higher compressive force on the surface of an inert solute than do typical organic liquids so that water squeezes-out hydrophobic solutes (232). More pertinent for the present discussion is that the Pratt-Chandler theory overestimates this compressive force and the original scaled particle model underestimates it(14, 15). The revised scaled particle model(135) lands in the middle and does a better job at describing this compressive force. Recent work(164) has studied these quantities over a much larger range of λ and confirmed the accuracy of the revised scaled particle model.

The reason for the differences between the scaled particle models and the Pratt-Chandler theory is associated with the known behavior $\rho_W G(\lambda) \sim p/RT$ for large λ. For the cases of first interest, $p/\rho_W RT \ll 1$. Since $G(\lambda)$ is initially one (1) and typically increases initially, $G(\lambda)$ decreases for large λ to achieve the small value $p/\rho_W RT$. In fact, this decreasing behavior obtains for λ >3 Å, approximately. Thus, for hard sphere solutes with $\lambda \gg 3$ Å the contact density can be small. This low pressure for a dense liquid is due to attractive forces between the solvent molecules. If the conditions are adjusted for liquid-vapor coexistence, then p is also the pressure of the coexisting vapor and p/RT would be the density of the vapor under the assumption that it can be treated as ideal. Under these conditions we can, therefore, say that a sufficiently large hard sphere solute nucleates a bubble of the vapor. These behaviors are built into the approximate scaled particle models but not into the Pratt-Chandler theory. These issues had been directly investigated for spherical model solutes moderately larger than canonical for methane(5); weak effects and were found for those cases and convincing models were developed(5).

PMF for stacked plates in water

This issue has been of particular interest recently because a previous calculation(233) studied the pmf between modeled stacked plates with exclusively repulsive interactions with water molecules. That work suggested that contact hydrophobic interactions in that case could be dominated by a dewetting event: the last two layers of water molecules intervening between parallel plates evacuated together.

Benzene-Benzene PMF

The comparable results for more realistically modeled benzene, or toluene, or other small aromatic solute molecule pairs are also interesting but more complicated(51, 197–200, 211, 212, 215). These molecules are slightly smaller than the stacked plates that were studied. In the first place, 'T'-shaped contact pairs are more probable for benzene than a stacked arrangement is. The opposite is true for toluene(212). This is also true for the gas-phase potential energy surface though the hydration seems to enhance this distinction(212) slightly. In the second place, variations in these pmfs(51, 197, 199, 200, 212, 215) are much smaller than for the modeled stacked plates(233). A dewetting transition is not obvious for the calculations with higher molecular realism. It may be the significance of any dewetting would be more obvious near transitional configurations such as the desolvation barrier region that separates contact from solvent-separated configurations. Though the hydration of neither of the high probability configurations discussed here seemed(51, 199, 200, 212, 215) remarkable in this way, the variation of the free energy in the desolvation barrier region might be unusual; this deserves further checking. How these complications are affected by the more complicated environment of an amino acid side chain, *e.g.,* phenyl alanine, in a hydrated protein is not known; the peptide backbone is, of course, highly polar. The hydrogen bonding possibilities of tyrosine or tryptophan side chains complicate things yet again. An interesting study of pairing of tryptophan-histidene side chains (215) suggested that hydration of these side chains results in stacked pairing near protein surfaces but 'T'-contacts in protein interiors. [Continuum dielectric models did not provide a rationalization of that observed tendency(215).] The variety of the results obtained suggested(215) "... the importance of the atomic details of the solvent in determining the free energy for the solute-solute interactions."

Theory of interface formation(163)

The development of the theory corresponding to the stacked plates data was initiated by Lum, Chandler, and Weeks; see Fig. 1 there(234). Subsequently(235–238), a focus has been the study of how the entropy dominated hydration free energies discussed above for inert gas solubilities change to the surface tension dom-

inated behavior expected for ideal mesoscopic hydrophobic species; see also(128). That behavior was explicitly built into the revised scaled particle model for hard sphere solutes decades ago(135); that model is known to be accurate for water(164) and for a simple liquid(235, 237). A fundamental niche for that theoretical work(163) is the development of a molecular description of the interface formation mechanism built into the revised scaled particle model at large sizes(163).

How these theoretical developments will accommodate heterogeneity of chemistry and structure that is typical of biomaterials, in contrast to the model stacked plates, is not yet established. A nice example of the issue of heterogeneity, absorption of water on activated carbon, was discussed recently by Müller and Gubbins(240). It is unreasonable to imagine that the biophysical applications will be simpler than this. It might be more appropriate at this stage of development to regard that Berkeley project as ambitiously directed toward an implicit hydration model(20) rather than an assertion of specific physical relevance of 'drying' to biomolecular structure(239). These problems require consideration of several distinct issues together. One such issue is the direct contributions of solute-solvent attractive interactions to hydration free energies for a specific structure(241). A second issue is the indirect effects of solute-solvent interactions in establishing structures and switching between structures as was initially anticipated(234). That switching can be sensitive to details of van der Waals attractive interactions(164, 242–245).

It is worthwhile attempting to articulate a down-to-earth view of the claims of Ref. (234) specifically. For biomolecules, there likely are uncommon transitional structures and conditions for which localized water occupancies can change abruptly. As these transitional structures become indentified, they will be interesting. Considering water-hydrocarbon liquid interfaces, not compromised by hydrophilic contacts, it is likely that these interfacial regions will be looser than adjoining bulk phases and more accomodating to imposition of hydrophobic species(146). Surfactants probably change that conclusion qualitatively(146). This is likely to be relevant to protein hydration and function. Most solute configurations, except for a few transitional structures, won't require specific acknowledgement of 'drying.' The claims to Ref. (234) don't seem to require modification of the discussion above on POTENTIALS OF THE MEAN FORCES AMONG PRIMITIVE HYDROPHOBIC SPECIES IN WATER that separated contact from non-contact configurations and entropy effects from the rest, and then suggested that the more poorly understood non-contact questions are likely to show the most variability. The specific claims of Ref. (234) and the general issues remain questions for research.

CONCLUDING DISCUSSION

This review has adopted a narrow theoretical focus and a direct style with the goal of identifying primitive conclusions that might assist in the next stage of molecular research on these problems. These theory and modeling topics haven't been reviewed with this goal recently and a review of the bigger topic of hydrophobic effects would not be feasible in this setting. More comprehensive and formal reviews of these topics are in progress and that must be my excuse for considering such a small subset of the work in this area. Nevertheless, some historical perspective is necessary in identifying valuable primitive conclusions.

One such conclusion is the rectification of the antique 'Pratt-Chandler theory'(1–16). This was an unexpected development because the advances reviewed above had bypassed stock integral equation theories. It may have been the stock aspect of the earlier approach (17) that caused the greatest confusion on this topic. There is no obvious point to doing that type of integral equation approximation again for the more complex solutes to which the theoretical interest has progressed. For the problems addressed, however, this amended Pratt-Chandler theory is now seen to be a compelling, approximate theory with empirical ingredients. The research noted above on *Theory of interface formation* and *Importance sampling to correct quasi-chemical models* emphasize that the treatment of those attractive force effects on the hydration problem by the Pratt-Chandler theory was less satisfactory than that of the scaled particle models.

Another primitive conclusion is that the scaled particle models(135, 138) have been the most valuable theories for primitive hydrophobic effects. This is due to the quantitative focus of those models. The quantitative focus of the scaled particle models permitted more incisive analyses(12–15, 135, 139, 140), in contrast to 'pictorial theories,' and those analyses have lead to significant advances in understanding of these problems. The connection from scaled particle models, to Mayer-Montroll series(10, 159), the potential distribution theorem(3, 160), and the quasi-chemical approach(11, 19–23) identifies a promising line for further molecular theoretical progress on these problems. Comparing Eqs. 4 and 5, the amended Pratt-Chandler theory is most appropriately viewed as a quasi-chemical theory. The anticipated theoretical progress will treat more thoroughly the effects of changes in temperature, pressure, and composition of the solution, including salt effects, and will treat neglected 'context' hydrophobicity(197) in detail. That work will study cold denaturation and chemical denaturation in molecular detail. That work will begin to discriminate hydrophobic effects in the cores of soluble proteins from hydrophobic effects in membranes and micelles. That work will begin to consider hydrophobic effects in nanotechnology with molecular specificity.

A natural explanation of thermodynamic signatures of hydrophobic hydration, particularly entropy convergence, emerges from these theoretical advances. How those temperature behaviors are involved in cold denaturation or the stability of

thermophilic proteins will be a topic for future research.

Much has been made of the 'Gaussian' character of results such as Fig. 2. The observation(1) best supporting this view can be explained as a cancellation of approximation errors(23); slight inaccuracies of a Percus-Yevick ('Gaussian') approximation are balanced by neglect of incipient interface formation for atomic sized solutes. In a number of other cases where these distributions have been investigated carefully simple parabolic models of results such as Fig. 2 are less accurate for thermodynamic properties and not only because of the influence of a second thermodynamic phase nearby. Nevertheless, quadratic models provide convenient, reasonable starting points for these analyses.

A final conclusion regards the better discrimination of contact and non-contact hydrophobic interactions. The contact hydrophobic interactions seem to express the classic picture of entropy dominance at lower temperatures. The non-contact interactions have more variability and are likely to be involved in more unusual effects such as pressure denaturation where a historical picture of hydrophobicity had been paradoxical.

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FIGURE LEGENDS

Figure 1 The isothermal compressibilities $\beta_T \equiv -\left(\frac{1}{\rho}\right)\left(\frac{\partial\rho}{\partial p}\right)_T$ along the liquid-vapor coexistence curve of several organic solvents compared to water(144) in common units. From top to bottom are n-heptane, carbon tetrachloride, benzene, and water. The compressibility is smaller for water than for these organic solvents, is less strongly temperature dependent, and has a minimum near 46° C. The critical temperatures of these organic solvents are all substantially less than the critical temperature of liquid water.

Figure 2 Distribution $\hat{p}_n$ for a isodiameter hard sphere solute in a hard sphere fluid at density ρd^3=0.8 and various models. The dots are simulation results(23) and the spread indicates a 67% confidence interval. The upper dashed curve is the Poisson distribution with the required mean $\langle n\rangle_0 = 4\pi\rho d^3/3$. The long-dashed curve next down is the primitive quasi-chemical model, Eq. 9(23). The solid line is an 'iterated' quasi-chemical theory that incorporates an empirical correlation correction(23) and provides a simple accurate description of these quantities for the hard sphere fluid. Note that the primitive quasi-chemical approximation is a good description of this distribution for n$\geq$1 but significantly overestimates p_0 at these densities.

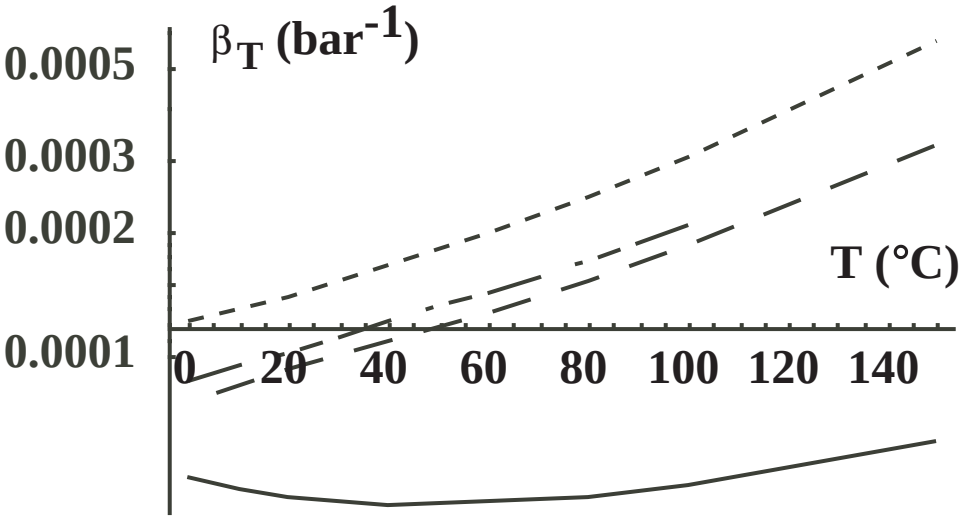

Figure 1:

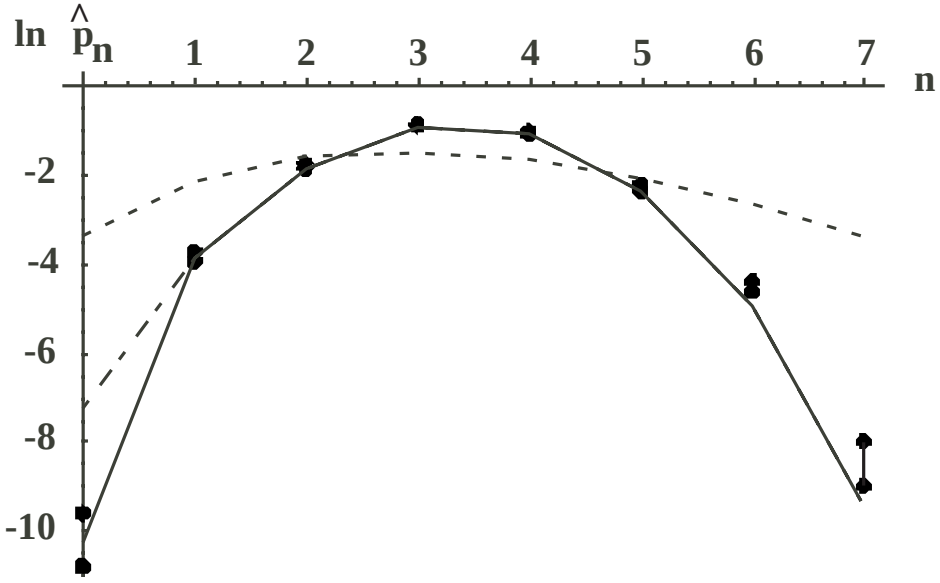

Figure 2: